

REMARKS

It is believed that this application has been amended in a manner that places it in condition for allowance at the time of the next Official Action.

Claims 19-39 are pending in the present application. Claim 39 has been amended to more particularly point out and distinctly claim the present invention.

In the outstanding Official Action, claims 19-23, 25-28, and 31-36 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable in view of claims 1, 2, and 6-11 of co-pending Application No. 09/913,596 ('596). This rejection is respectfully traversed.

It is believed that the outstanding Official Action fails to meet its burden in showing that the claims of the present invention are obvious in view of claims 1, 2, and 6-11 in the '596 application.

Claims 1, 2, and 6-11 in the '596 application are directed to processes for oxidizing cellulose, oxidized cellulose derivatives, and cellulose derivatives. The claimed invention relates to oxidizing a non-cellulose primary alcohol into an oxidized carbohydrate. As the claims of the '596 application are all directed to cellulose, applicants believe that the claimed invention cannot be obvious in view of the cited claims.

While the outstanding Official Action contends that it is permissible to use the specification in determining what is included in the invention defined by the claims, applicants note that it is not permissible to use the disclosure of the present application as prior art. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). In imposing the double patenting rejection, applicants believe that the Examiner impermissibly uses the disclosures of the applications.

For example, the outstanding Official Action concedes that the '596 application relates to cellulose and does not refer to oxidizing primary alcohols in the claims, yet the Official Action contends it is known in the art and dictated in the specification that the primary alcohol function of the cellulose is what is actually being oxidized to a corresponding aldehyde (see page 4 of the outstanding Official Action). Thus, it is believed that the Official Action clearly relies on passages from the disclosure that do not pertain to the claims. As a result, it is believed that the Official Action improperly relies on the disclosure of the two applications. Moreover, applicants note that the Official Action fails to provide any additional evidence to support this assertion.

The outstanding Official Action also contends that it would be obvious to one of ordinary skill in the art to incorporate specific enzymes which are capable of oxidation. Moreover, the Official Action alleges that the compositions as

claimed are obvious variations. The Official Action also contends that one of ordinary skill in the art would find the process steps as being the same. However, applicants believe that the Official Action also fails to substantiate these assertions and traverse the unsupported conclusions of the Official Action.

Thus, in view of the above, applicants believe that claims 19-23, 25-28 and 31-36 are not obvious in view of the claims of the '596 application. Applicants respectfully request that the provisional obviousness-type double patenting rejection be withdrawn.

In the outstanding Official Action, claim 39 was rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. It is believed that the present amendment obviates this rejection.

The outstanding Official Action alleged that the term "derivative" rendered the claim indefinite. In the interest of advancing prosecution, claim 39 has been amended so that this term is no longer recited in the claim. Thus, it is believed that claim 39 is definite to one of ordinary skill in the art.

Claims 19-39 were rejected under 35 USC §103(a) as allegedly being unpatentable over VIIKARI et al. (WO 99/23117). This rejection is respectfully traversed.


It is believed that the VIIKARI et al. publication fails to qualify as prior art. The VIIKARI et al. publication was published in May of 1999. However, the present application claims priority to the priority document EP 99200536.3 filed on February 24, 1999. The priority document is enclosed with this amendment for the Examiner's convenience. Thus, it is believed that the VIIKARI et al. publication fails to anticipate or render obvious the claimed invention.

In view of the present amendment and the foregoing remarks, therefore, it is believed that this application has been placed in condition for allowance, with claims 19-39, as presented.

Attached hereto is a marked-up version of the changes made to the claims. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 39 has been amended as follows:

--39. (amended) An oxidized carbohydrate, said carbohydrate being selected from disaccharides, oligosaccharides and polysaccharides of the beta-glucan types, containing at least 1 cyclic monosaccharide chain group carrying a carbaldehyde group per 25 monosaccharide units and per average molecule, [or a chemical derivative thereof and] further containing carboxymethyl groups.--

Novel cellulose-type carbohydrate aldehydes

[1] The invention relates to carbohydrate aldehydes obtainable by selective oxidation of alcohols. The oxidation is carried out using an oxidising agent in the presence of a catalytic amount of a di-tertiary-alkyl nitroxyl compound, especially 2,2,6,6-tetra-
5 methylpiperidin-1-oxyl (TEMPO).

[2] Such a process in which TEMPO is reoxidised by chemical means is known from a review by De Nooy in *Synthesis* 1996, 1153-1174.

[3] It was found according to the invention that the oxidation of alcohol functions, especially primary alcohol functions, can be carried out without using chlorine-based
10 oxidising agents and with the use hydrogen peroxide or oxygen as the ultimate oxidising agent. The oxidation according to the invention is performed using enzymes and/or metal complexes. This oxidation, when carried out on primary alcohols, surprisingly results in formation of aldehydes, without further oxidation to carboxylic groups under appropriate conditions. The aldehydes may be present in the (hemi)acetal form and related structures.
15 An adaptation of the oxidation of the invention can be used to oxidise secondary alcohols, especially carbohydrates, to keto derivatives. The process of the invention is further defined by the characterising features of the appending claims.

[4] In the following description, reference is made to TEMPO only for the sake of simplicity, but it should be understood that other di-tert-alkyl nitroxyls, such as 2,2,5,5-
20 -tetramethylpyrrolidine-N-oxyl (PROXYL) and 4-hydroxy-TEMPO and derivatives thereof and those described in WO 95/07303 can be substituted for TEMPO. These di-tert-alkyl nitroxyls are especially suitable for selectively oxidising primary alcohols to aldehyde functions, in particular in the presence of secondary alcohol functions that should not be oxidised. Less sterically hindered nitroxyls, such as 4,4-dimethyl-
25 oxazolidine-N-oxyl (DOXYL), are suitable for preferentially oxidising secondary alcohols to keto functions, for example in the production of keto cellulose or keto starch.

[5] A catalytic amount of nitroxyl is preferably 0.1-2.5% by weight, based on the primary alcohol, or 0.1-2.5 mol% with respect to the primary alcohol. The nitroxyl may also be immobilised, e.g. by coupling of the hydroxyl group of 4-hydroxy-TEMPO to
30 a suitable carrier, or in the form of a polymeric nitroxyl such as:

$-\text{[(CH}_3\text{)}_2\text{C-NO-C(CH}_3\text{)}_2\text{-A-]}_n\text{-}$, wherein A may be an alkylene group and/or a hetero-

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atom, and n is a number from e.g. 10 up to several hundreds.

[6] The products can result from oxidation of primary alcohols to the corresponding aldehydes. If required the primary products can be further oxidised to the corresponding carboxylic acids by using known oxidising agents such as hypochlorite, chlorite, hydrogen peroxide or by using TEMPO-mediated oxidation under more vigorous conditions such as an increased temperature e.g. from 40–80 °C, or for prolonged exposure to the reaction conditions.

[7] The carbohydrates may be oligosaccharides and polysaccharides. The oligo- and polysaccharides are of the β -glucan type, including cellulose and cellulose derivatives and hydrolysates or of the furanoid pentosan type (hemicelluloses including xylans and the like), i.e. types that correspond to wood-derived polysaccharides.

[8] A distinct group of compounds suitable for oxidation with the present process consists of hydroxyalkylated carbohydrates such as hydroxypropyl or hydroxyethyl (hemi)cellulose, which result in an alternative way for producing formylalkyl (hemi)-celluloses. Other suitable substrates in which at least a part of the (6-) hydroxymethyl groups are intact, include for example (2- and 3-) carboxymethyl carbohydrates.

[9] The oxidation of carbohydrates containing primary hydroxyl groups results in the corresponding carbohydrates containing aldehydes and, if desired, to carboxylic acids, with intact ring systems. These products are useful intermediates for functional carbohydrates wherein the aldehyde groups are further reacted with e.g. amine compounds and the like. They are also useful intermediates for crosslinked carbohydrates, in which the aldehyde groups are further reacted with e.g. diamine reagents.

[10] The catalysts to be used according to the invention are oxidoreductases or other enzymes that are capable of oxidation in the presence of a suitable redox system. Oxidoreductases, i.e. enzymes capable of oxidation without the presence of further redox systems, to be used in the process of the invention include peroxidases and oxidases, in particular polyphenol oxidases and laccase. Certain hydrolases, such as phytase, can be used when a further redox system is present such as a metal complex, e.g. vanadate. Metal complexes as such, without an enzyme protein, can also be used: examples include

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chlorite as an ultimate electron acceptor.

[11] Peroxidases (EC 1.11.1.1 - 1.11.1.11) that can be used according to the invention include the peroxidases which are cofactor-independent, in particular the classical peroxidases (EC 1.11.1.7). Peroxidases can be derived from any source, including plants, bacteria, filamentous and other fungi and yeasts. Examples are horse-radish peroxidase, soy-hull peroxidase, myelo peroxidase, lactoperoxidase, *Arthromyces* and *Coprinus* peroxidases. Several peroxidases are commercially available. The peroxidases require hydrogen peroxide as an electron acceptor.

[12] Polyphenol oxidases (EC 1.10.3.1) include tyrosinases and catechol oxidases, such as lignine peroxidase. Suitable polyphenol oxidases may be obtained from fungi, plants or animals. The polyphenol oxidases require oxygen as an electron acceptor. Laccases (EC 1.10.3.2) are sometimes grouped under the polyphenol oxidases, but they can also be classified as a distinct group, sometimes referred to as p-diphenol oxidases. Laccases can be derived from plant sources or from microbial, especially fungal, sources. The laccases also require oxygen as an electron acceptor.

[13] The process for producing the aldehydes of the invention can be performed under relatively mild conditions, e.g. at a pH between 2 and 10, and at a temperature between 15 and 60°C (both depending on the particular enzyme or metal complex). The reaction medium can be an aqueous medium, or a homogeneous mixed medium, e.g. of an alcohol/water or an ether/water mixture, or a heterogeneous medium, e.g. a mixture of water and a water-immiscible organic solvent such as a hydrophobic ether, a hydrocarbon or a halogenated hydrocarbon. In the latter case, the enzyme and/or the nitroxyl and the oxidising agent may be present in the aqueous phase and the alcohol substrate and the aldehyde or ketone product may be present in the organic phase. If necessary, a phase transfer catalyst may be used. This type of reaction is suitable e.g. for the oxidation of steroids. The reaction medium can also be a solid/liquid mixture, in particular when the enzyme or the nitroxyl are immobilised on a solid carrier. A heterogeneous reaction medium may be advantageous when the substrate or the product is relatively sensitive or when separation of the product from the other reagents may present difficulties.

[14] The invention pertains to novel carbohydrate oxidation products and derivatives thereof, which can be obtained with the process of the invention. These include

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polysaccharides in which at least 1 hydroxymethyl per 100, especially per 50 or even per 25, monosaccharide units has been converted to a carbaldehyde group, whether or not in hemiacetal or similar form, with the proviso that on average each molecule contains at least 1 carbaldehyde group other than a possible (hemiacetalised) aldehyde group at the reducing end of an oligo- or polysaccharide. The carbaldehyde group is preferably present in chain (backbone) units, rather than in branch units. In the products of the invention, the monosaccharide rings that carry the carbaldehyde group are largely intact, and the number of aldehyde groups is greater, especially more than two times greater, than the number of carboxyl groups (other than introduced carboxyalkyl groups). Such product are not accessible by prior art oxidation methods, which invariably lead to at least partial further oxidation to carboxyl groups. The only common carbohydrate derivatives having a predominant content of aldehyde groups are periodate-type oxidation products of starch, cellulose and the like, in which the rings bearing the aldehyde groups are broken. The aldehyde carbohydrates covered by the present invention are of the cellulose type or furanoid pentosan type (or derivatives such as carboxymethylated, alkylated, hydroxyalkylated cellulose and xylans).

[15] The novel derivatives of the invention are very suitable as thickeners, viscosifiers, stabilisers for emulsions and the like, and especially as starting materials for further functionalisation, especially with alcohols, amines, and other agents capable of coupling with an aldehyde function. Such agents include crosslinking agents (diamines, diols and the like), which can be used to crosslink the carbohydrates or to couple them to amino acids, proteins, active groups etc.

[16] The invention also pertains to derivatives obtained by coupling of the aldehyde carbohydrates described above with e.g. amines as defined in the appending claims.

25 [17] **Example: Production of 6-aldehyde cellulose**

One gram of totally bleached sulphate pulp fibers (SCA Östrand mill, dry weight) was suspended in 100 ml of water. To this suspension were added 18 mg of TEMPO (0.1 mmol) and 9 mg of peroxidase (HRPO), type VI (290 units/mg). The pH was adjusted to 5.1 with aqueous acetic acid (0.1 M). A hydrogen peroxide solution (1.5 ml 30% in 50 ml) was added stepwise (30–50 µl every 2 minutes) for 8 hours. After peroxide addition the pH decreased, but it returned to its original value (5.5) after a few moments;

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therefore, no pH adjustment was necessary during the reaction. After 21 h a sample was analysed by addition of hydroxylammonium chloride. The pH of the mixture was brought to pH 11.6 by addition of aqueous NaOH, and back-titrated with 0.1 M HCl. According to this analysis, the sample contained 26% of C6-aldehyde cellulose.

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Claims

1. An oxidised carbohydrate, the carbohydrate being selected from β -glucans and pentosans, containing at least 1 cyclic monosaccharide chain group carrying a carbaldehyde group per 50 monosaccharide units and per average molecule.
2. An oxidised carbohydrate according to Claim 1, which contains 1 to 50 cyclic monosaccharide chain group carrying a carbaldehyde group per 50 monosaccharide units and per average molecule.
3. An oxidised carbohydrate according to Claim 1 or 2, which contains β -1,4-6-oxo-anhydroglucose units.
4. An oxidised carbohydrate according to any one of Claims 1-3, containing at least 5, especially at least 10 monosaccharide units per average molecule.
5. A carbohydrate derivative according to any one of the preceding Claims, in which derivative at least a part of the carbaldehyde groups has been converted to a group with the formula $-\text{CH}=\text{N}-\text{R}$ or $-\text{CH}_2-\text{NHR}$, wherein R is hydrogen, hydroxyl, amino, or a group R^1 , OR^1 or NHR^1 , in which R^1 is C_1-C_{20} alkyl, C_1-C_{20} acyl, a carbohydrate residue, or group coupled with or capable of coupling with a carbohydrate residue.
6. A carbohydrate derivative according to any one of the preceding Claims, in which derivative at least a part of the carbaldehyde groups has been converted to a group with the formula $-\text{CH}(\text{OR}^3)-\text{O}-\text{CH}_2-\text{COOR}^2$ or $-\text{CH}(-\text{O}-\text{CH}_2$

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Abstract

Oxidised carbohydrates selected from β -glucans and pentosans are described, containing at least 1 cyclic monosaccharide chain group carrying a carbaldehyde group per 50 monosaccharide units and per average molecule. The aldehyde are obtainable by oxidation of a carbohydrate (cellulose) using an oxidising agent and a catalytic amount of a nitroxyl compound, in the presence of a metal complex and/or an enzyme capable of oxidation.